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Hemorrhagic transformation of acute ischemic stroke is limited in hypertensive patients with cardiac hypertrophy

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ABSTRACT

Background: It has been clearly demonstrated that hypertension and one of its main evoked effects, cardiac hypertrophy, are independent risk factors for ischemic stroke. However, the ischemic brain lesions can further be affected by a second wave of injury characterized by hemorrhagic transformation (HT) of the primary ischemic lesion, which significantly aggravates the clinical outcome. So far, the risk factors that could affect such a transition in hypertensive patients are still unclear.
Methods: In this study, we investigated whether in hypertensive patients the concomitant presence of cardiac hypertrophy can affect the transition of ischemic brain lesions toward HT.
Results: Our analysis was focused on a population of hypertensive patients admitted to our Acute Stroke Unit. The hypertensives with acute ischemic stroke suffering of HT were 18% of the sample. In these latter, the prevalence of cardiac hypertrophy was significantly lower than in those spared by HT as also shown by the levels of left ventricular mass index (LVMI) that were significantly higher in patients spared by HT. More important, cardiac hypertrophy was protective even from symptomatic HT.
Conclusion: Here we show that hypertensive patients with cardiac hypertrophy have less probability to develop HT during an acute episode of ischemic stroke. These results could help to identify patients with lower risk of spontaneous HT and that could have better beneficial effects from thrombolytic therapy during acute ischemic stroke.

1. Introduction

Stroke is a major health problem, being the third leading cause of death in industrialized countries and the most frequent cause of permanent disability in adults worldwide. Hypertension, known to cause significant damage to organs such as the heart, kidney, eye and vessels, is the main risk factor for stroke [1]. Moreover, high blood pressure imposes continuous mechanical challenge on the cardiovascular system leading to hypertrophic remodelling of both cardiac and vascular tissues. It is now increasingly recognized that this architectural cardiovascular remodelling can be considered a double-faced process, being both a sign of target organ damage evoked by hypertension itself and a compensatory adaptive process to hemodynamic overload [2–4].

Previous studies demonstrated that not only hypertension, but also cardiac hypertrophy is an independent risk factor for ischemic stroke [5,6]. Moreover, we also found that cardiac hypertrophy is associated to an asymptomatic cerebral ischemic damage in hypertensive patients [7], thus leading to hypothesize that when the hypertensive conditions are more sustained, likely to induce a hypertrophic remodelling, brain ischemic injury is favoured. However, it should also be noticed that the cerebrovascular ischemic event in hypertensive patients, is not only delimited to the acute onset of reduced supply of nutrients to the brain but can also be characterized by a series of pathophysiological changes that further affect the prognosis [8–10]. A better knowledge of how risk factors affect also the evolution of ischemic brain lesions, beyond the acute event itself, is very important for clinical management and prognosis.

Actually, in a relevant subset of hypertensive patients ischemic brain lesions can further be affected by a second wave of injury characterized by disruption of the blood brain-barrier (BBB) and hemorrhagic transformation (HT) of the primary ischemic lesion, which significantly aggravates the clinical outcome [11,12]. Some risk factors for HT, beyond hypertension itself, like aging, large brain lesions, high levels of blood glucose and thrombolytic treatment, have already been identified [13–14]. However, whether the presence of cardiac hypertrophy, one of

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the typical hallmarks of sustained hypertension, can affect the transition of ischemic brain lesions toward HT remains unknown. For this reason, we analyzed retrospectively the data of hypertensive patients admitted to our Clinical Unit for Acute Stroke, focusing our attention on the role of hypertrophic cardiac remodeling in the hemorrhagic evolution of ischemic stroke.

2. Methods

2.1. Study population

We performed a blinded retrospective analysis of 99 consecutive hypertensive patients who were admitted to the Stroke Unit of IRCCS Neuromed from February 2008, with an acute ischemic stroke. Data were collected and analyzed in accordance with the principles stated in the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001. Demographics, clinical data, risk factors for stroke and imaging findings of all the patients were collected using a standardized data record form. Two independent clinicians reviewed assessment of all the clinical variables and two blinded investigators reviewed the Magnetic Resonance Imaging (MRI)/Computed Tomography (CT) scans imaging, in order to determine the presence of HT [15,16]. Eligible patients were divided into 2 groups according to the presence or absence of HT during hospitalization.

2.2. Radiological and clinical evaluation

The clinical status of the patients was defined by the National Institute of Health Stroke Scale (NIHSS), at admission and during the hospitalization period. Patients underwent MRI/CT scans at admission, at day 1 and at any clinical worsening. HT was diagnosed using follow-up CT scan or gradient echo MRI (mean HT onset time was 84 ± 22 h after the primary ischemic lesion).

HT was radiologically and symptomatically subcategorized, according to the recommendations of the European Cooperative Acute Stroke Study (ECASS) [17]. In particular, the radiological categories for HT were as follows: 1) haemorrhagic infarct type 1 with small petechiae along the margins of the infarct (HI1) and type 2 with more confluent petechiae within the infarct area (HI2); Parenchimal hematoma type 1 defined as a hematoma in less than 30% of the infarcted area (PH1) and type 2 with hematoma in more than 30% of the infarcted area (PH2).

As regards the clinical categories of HT, they were defined as asymptomatic HT (asHT) with no clinical worsening of the NIHSS score, despite the radiological presence of HT, and symptomatic HT (sHT) with any clinical worsening, detected as an increase of NIHSS score, associated to the radiological presence of HT.

At the admission, patients underwent cerebral MRI and/or CT scans, neurological assessment, blood sampling, echocardiography, and blood pressure measurement. Moreover, an anamnestic questionnaire recorded age, gender, weight and height, smoking habits, previous diseases, hyperlipidemia, diabetes, previous transient ischemic attack (TIA) or stroke, myocardial infarction, atrial fibrillation, and pharmacological treatments. From blood samples, we considered glucose levels, triglycerides, low density lipoprotein (LDL), high density lipoprotein (HDL) and total cholesterol, albumin, platelets count, fibrinogen, international normalised ratio (INR) and activated partial thromboplastin time (aPTT), total white blood cells, neutrophils, lymphocytes and monocytes. Diuretics, angiotensin receptor blockers, α and β blockers, Ca-antagonists and ACE-inhibitors were included as antihypertensive treatments, while aspirin and ticlopidine as antiplatelet therapy.

2.3. Echocardiographic analysis

The overall 1-dimensional left ventricle (LV) measurements and the 2-dimensional views were obtained according to the American Society of Echocardiography guidelines [18]. In particular, Left Ventricular Mass (LVM) was calculated using the Devereux's formula: $LVM\ (g) = 0.8 \times [1.04\ (LVIDD + IVS + PWT)^3 - LVIDD^3] + 0.6$, where LVIDD is left ventricular internal diameter at end-diastole, IVS is thickness of interventricular septum at end-diastole and PWT is posterior wall thickness at end-diastole. LVM was normalized for the height elevated to 2.7 (LVMI). Left ventricular hypertrophy (LVH) was defined as $LVMI > 50\ g/m^{2.7\ 7}$ [19]. Then we calculated the Relative Wall Thickness (RWT) at end-diastole as 2 PWT/LVIDD.

Patients were characterized according to their cardiac structure, with a partition value of 0.44 for RWT. Patients with increased LVMI and increased RWT were considered to have LV concentric hypertrophy, and those with increased LVMI and normal RWT were considered to have LV eccentric hypertrophy, while those with normal LVMI were considered normal.

Two blinded cardiologists reviewed the echocardiographic analyses, in order to assess the presence and the type of cardiac hypertrophy.

2.4. Statistical analyses

Based on previous studies assessing the relationship between left ventricular mass and the incidence of acute cerebrovascular events in hypertensive patients [6], and hypothesizing an incidence of HT of 17% in the first week [11], the power analysis calculation estimated 18 cases in order to achieve an alpha of 0.05 and a beta power of 0.85.

Depending on the type of variables, the baseline characteristics of patients were presented as numbers (%) or means ± SD. The first step of analysis was aimed at identifying predictors of HT. Univariate tests were used to compare clinical characteristics on admission, pre-existing risk factors, neuroradiological imaging, therapies administered (before admission and in-hospital treatments), haematological parameters of HT versus non HT hypertensive patients with acute ischemic stroke. Means were compared using Student's T test for normal-distributed and Mann–Whitney U test for not normal distributed continuous variables. Shapiro–Wilk Test was used to assess the normality of continuous variables. Categorical data were compared using Fisher exact Chi-Square test.

Stepwise logistic multiple regression analysis was performed in order to better understand the relation between HT and cardiac hypertrophy using different adjusted models: model 1 was adjusted for age and gender; model 2 was further adjusted for the factors already established as significant predictors of HT in the univariate analysis.

All statistical analyses were performed with SPSS 21 (IBM, USA) and significance level was set at two-sided P value <0.05.

3. Results

3.1. Clinical characteristics of patients

Among the 99 patients with acute ischemic stroke, 52 were men and 47 women. Their mean age was 69 (±14) years. The HT of ischemic lesions was diagnosed in 18% of subjects, and such prevalence is in accordance with previously published reports [11].

The characteristics of patients with and without HT are shown in Table 1. Average age, proportion of gender, anamnestic variables, systolic and diastolic blood pressure on admission, area of ischemic lesion and neurological evaluation. Treatment before admission and treatment in-hospital are listed in Table 2, while laboratory variables are reported in Table 3.